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CANNABIELSOIC ACIDS

ISOLATION AND SYNTHESIS BY A NOVEL OXIDATIVE CYCLIZATION

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Abstract—Two tricyclic dihydrobenzofuran cannabinoids, cannabielsoic acids A (**4a**) and B (**5a**) were isolated from hashish. Their structures were elucidated by chemical transformations and from spectral data. Cannabielsoic acid A was synthesized from cannabidiolic acid by an oxidative cyclization in the presence of air under irradiation, or with manganese dioxide.

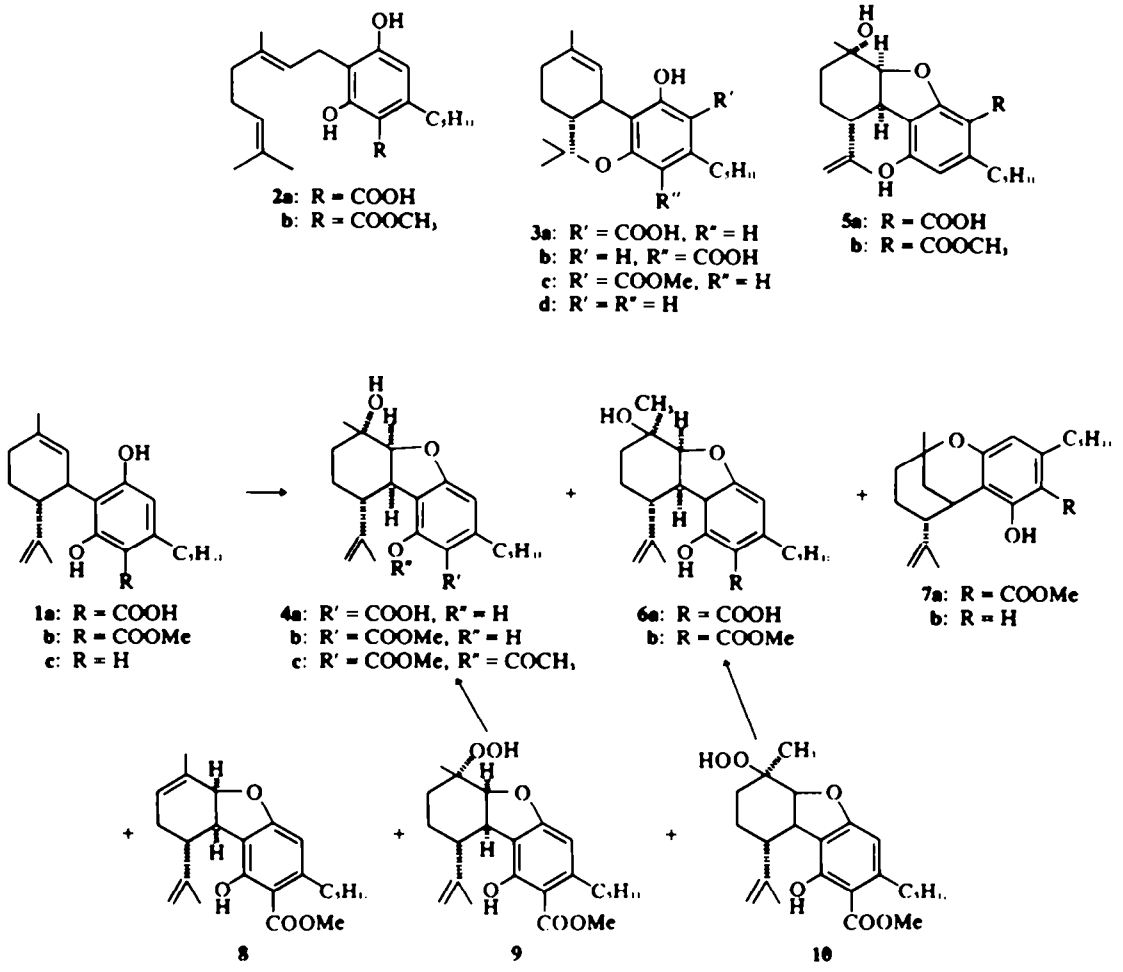
Most of the natural cannabinoids can be extracted from cannabis products (hashish, marihuana etc) with petroleum ether. Hence a considerable amount of work has been devoted to chemical and pharmacological investigations of this extract.[1] Some years ago we noted that extraction with benzene of the solid residue of the petroleum ether treatment gave a solution, which though pharmacologically inactive, contained compound(s) which on gas chromatography had the same retention time as the active Δ^1-THC. Hence we undertook an investigation of this benzene-extractable fraction.[2]

Chromatography of this fraction on silica gel showed that it consisted mainly of the known[1] cannabidiolic (**1a**) cannabigerolic and (**2a**) and Δ^1-THC A (**3a**) acids and a small amount of a mixture of additional acids which was further separated and purified by preparative thick layer chromatography. Cannabielsoic acid A (**4a**) and B (**5a**)† thus isolated represented 0·08% and and 0·04% of the content of hashish. A more facile method of isolation was found to be by column chromatography of the mono methyl esters **4b** and **5b**.

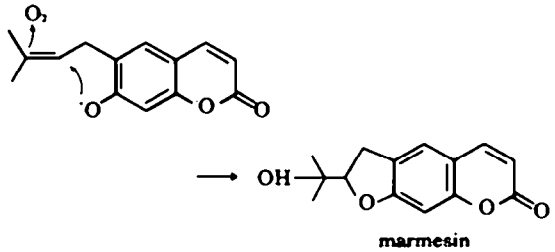
Cannabielsoic acid A methyl ester (**4b**), an oil, has a molecular weight of 388 *m/e* which differs by 16 mass units from that of cannabidiolic acid methyl ester (**1b**) or Δ^1-THC acid methyl ester (**3c**) (372 *m/e*) i.e. it represents a more highly oxygenated cannabinoid. The NMR spectrum of **4b** indicates the presence of only a terminal methylene group and *one* vinylic methyl group [as compared to a terminal methylene group and an olefinic proton, as well as *two* vinylic Me groups in cannabidiolic acid methyl ester (**1b**)]. It also possesses only one OH group which can be acetylated, a Me group (which can be assumed to be α to oxygen) at δ, 1·44 and a proton (presumably α to oxygen) which appears as a doublet at 4·12. A further proton signal (a double-doublet) appears at 3·38. We attribute this signal to the C-3 proton. Irradiation at 3·38 collapses the signal at 4·12 to a singlet; irradiation at 4·12 collapses the signal at 3·38 to a doublet. These double resonance experiments indicate that the protons with signals at 3·38 and 4·12 are on adjacent carbons. The OH group is H- bonded, as evidence by its very low field signal (at 11·28). The most plausible structure (except for stereochemistry) which fits the above data is **4b**.

The crystalline cannabielsic acid B, methyl ester (**5b**), m.p. 58–60° has the same molecular weight as **4b** and an almost identical NMR spectrum. However, the proton signal of the acetylable OH group appears at 5·75. We interpret this difference as indicating that in **4b** the carbomethoxyl group is adjacent and H- bonded to the phenolic OH, while in **5b** it is adjacent to the etheric oxygen. This is supported by IR data. In **4a** the CO of the carboxyl group is at 1630 cm^{-1} while in **5a** it is at 1725 cm^{-1}; in **4b** it is at 1660 cm^{-1} while in **5b** it is at 1720 cm^{-1}. The same phenomenon has been observed[4] in the IR spectra of THC acids A (**3a**) and B (**3b**). In the former (**3a**) the carboxyl group CO absorbs at 1615 cm^{-1} while in the later (**3b**) it is at 1710 cm^{-1}. We have suggested that in **3b** there is loss of

†The cannabiels oic group of compounds is thus named in memory of the late Miss Elsa Boyanova, who isolated these compounds from cannabis.



*Naturally occuring furans such as balfourdine,[7] vaginol,[8] marmesin,[9] columbianetine,[8] mamea compounds[8] and others are probably formed in Nature by this pathway. Brown *et al.*[10] have reported biosynthetic data (conversion of umbelliferone into marmesin) which is in accordance with this suggestion. They have proposed a pathway which assumes the formation of epoxy intermediates. However, the possibility of existence of radical intermediates rather than epoxy ones has not been eliminated. In view of the facile synthesis *via* radical intermediates of **4a** from **1a** (see text), intuitively, we prefer a radical biogenetic route.



coplanarity of the CO group and the aromatic ring due to steric hindrance i.e., the IR absorption of the CO group is only slightly influenced by the aromatic conjugation. In **3a** this effect is minimized apparently by H-bonding with the free phenolic group. We now suggest that the same relationships govern the IR spectral properties of the two cannabielsoic acids **4a** and **5a**. The UV spectra of these two acids also differ: In **4a** there is a peak at 269 mμ (ϵ, 8720), while in **5a** it is at 257 mμ (ϵ, 4850). Not surprisingly a similar shift is observed[4] in the THC acids: 260mμ (ϵ, 7900) in **3a**; 250 mμ (ϵ, 3210) in **3b**.

Structures **4** and **5** are based on the assumption that the cannabielsoic acids possess a normal cannabinoid skeleton, being biogentically derived from cannabidiolic acid (**1a**). A dihydrofuran ring (formed by ring closure of one of the phenolic groups of **1a** with the C-2 carbon of the terpene moiety) and a tertiary hydroxyl group at C-1 easily explain all the novel spectral features.*

The isolation of the cannabielsoic acids is

tedious. Hence, in order to fully establish the proposed structures and provide sufficient material for further investigations, we decided to synthesize this novel group of compounds. Fortuitously we were simultaneously engaged in an investigation of irradiations under various conditions of cannabidiolic acid (**1a**). Our interest in these reactions stemmed from our previous[11] photochemical investigation of cannabidiol (**1c**), which led to Δ^1-THC (**3d**) in addition to other novel and unexpected compounds.* Some of the products obtained from the irradiation of **1a** were shown to be of a different type than those obtained from **1c** and ultimately led to a facile synthesis of cannabielsoic acids. The best conditions found for this reaction were irradiation of **1a** in cyclohexane, with oxygen being bubbled throughout the reaction. Two different routes were followed for the isolation and identification of the products:

(i) The mixture obtained was reduced with sodium bisulphite. On preparative TLC two isomers were isolated: cannabielsoic acid A, **4a** (17%), identified by direct comparison with an authentic sample, and 1-iso-cannabielsoic acid, **6a** (16%) m.p. 162–5°.

(ii) The hydroperoxides in the reaction mixture were not reduced; however, in order to achieve a more facile separation the mixture was esterified with diazomethane. On preparative TLC eight compounds were isolated, seven of which were identified: Δ^8-iso-THC acid, methyl ester (**7a**) the dehydrated cannabielsoic acid methyl ester derivative **8**, the methyl ester of the starting material (**1b**), the peroxides **9** and **10**, cannabielsoic acid methyl ester (**4b**) and 1-iso-cannabielsoic acid methyl ester (**6b**).

We base our structural assignments on the following data:

Dehydration of cannabielsoic acid methyl ester (**4b**) with thionyl chloride gave essentially one product (**8**), while the isomer **6b** yielded a complicated mixture from which in addition to a small amount of **8** we were able to isolate a fraction, which on the basis of its NMR spectrum, was shown to be a mixture of compounds **11a** and **11b**. We interpret these dehydration experiments as indicating that the 1-hydroxyl group in **4b** is axial while in **6b** it is equatorial. It has been demonstrated by Barton *et al.*[13] that a tertiary, axial hydroxyl group α to a methyl group gives mainly an endocyclic olefin while the equatorial isomer produces a mixture containing the exocyclic olefin.

The above assignment is supported by NMR data. The two isomers, **4a** and **6a**, have almost identical spectral properties. However, the axial C_1–H in **4a** (in which the C_1 OH group is axial) is at δ 3·38, while in **6a**[1] (in which the C_1 OH group is equatorial and the C_1 Me group is axial) is at 3·30. The deshielding influence of an axial *hydroxyl* group on an axial proton on a γ carbon has been assumed to be stronger than that of an axial *methyl* group.[14]

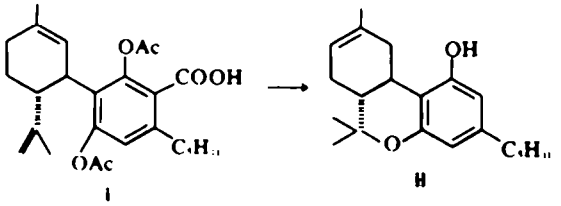
The synthetic correlation with cannabidiolic acid defines the relative and absolute stereochemistry of **4b** and **6b** at the chiral centers C_1 and C_4. The hydrogens on C_2 and C_3 are *cis*. This is deduced from the fact that radical or ionic processes which form related tricyclic dihydrobenzofuran systems (*cf* Pumerer's ketone)[15] give the more stable *cis*-compounds.[16] This is also supported by the coupling constants (ca 5–6 Hz) observed in all compounds of the cannabielsoic series. These values are in accordance with the coupling constants recorded for *cis* protons on adjacent carbon atoms in dihydrobenzofuran systems.[17] By contrast in dihydrobenzofurans in which the corresponding protons are *trans* the coupling constants are *ca* 2–3·3 Hz.[17]

Compounds **9** and **10** are peroxides. They give a positive potassium iodide–starch test. Their molecular weights (mass spectra) are higher by 16 mass units than those of the methyl esters of the cannabielsoic acids. Treatment with sodium bisulphite reduced peroxide **9** into cannabielsoic acid A methyl ester (**4b**) and reduced **10** into **6b**. The same reduction is achieved by heating or by irradiation.

Compound **7a** has a molecular weight (372 *m/e*) equivalent to that of the methyl ester of the starting material (**1b**). It differs from **1b** in the NMR spectrum: **7a** shows only one olefinic Me group and two (rather than three) olefinic protons. This spectrum is closely related to that of Δ^8-iso-THC (**7b**).[18] The formation of **7a** on irradiation of cannabidiolic acid was expected as we have reported that irradiation of cannabidiol (**1c**) produced **7b**.[11]

As the above described dehydration experiments are important for the elucidation of the stereochemistry at C_1 of the cannabielsoic acids we investigated parallel reactions in the dihydro series. Reduction of cannabielsoic acid methyl ester (**4b**) gave **12** which on dehydration with thionyl chloride in pyridine gave essentially *one* compound (**13**). By contrast **14** (the reduction product of **6b**) in which the tertiary OH group is equatorial, on dehydration under identical conditions gave a complicated mixture. Two products were obtained: compound **13** and a mixture of **15a** and **15b**. These experiments

*In a thesis,[12] the conversion on irradiation of cannabidiolic acid diacetate (I) into Δ^8-THC (II) is reported. This unusual reaction which involves 5 separate steps could not be reporduced in our laboratory.



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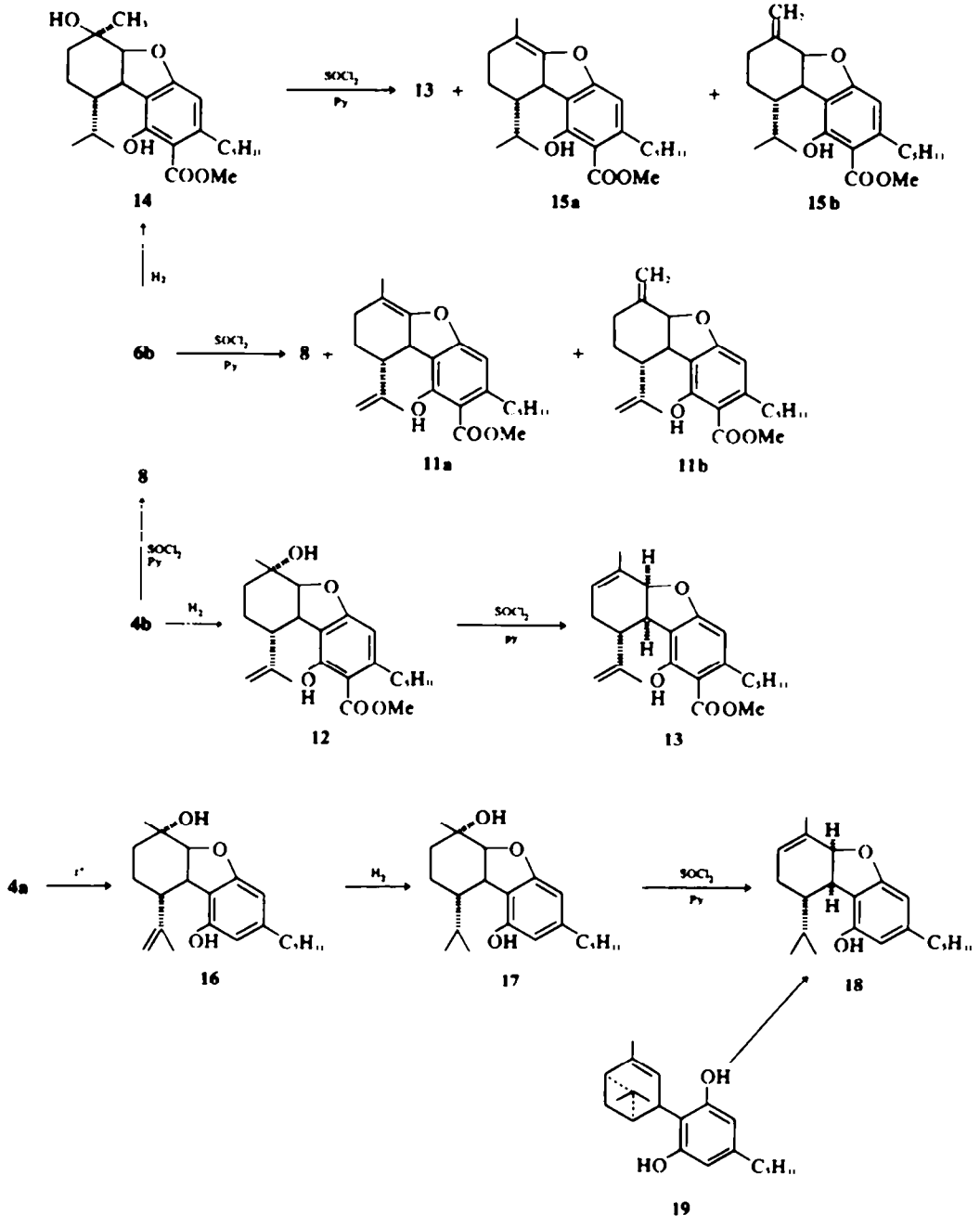


are fully compatible with the stereochemical assignments put forward in this paper (see above).

A further correlation with a totally synthetic product was achieved as follows: Cannabielsoic acid A (**4a**) was decarboxylated in a rather poor yield by distillation under reduced pressure. The decarboxylated product (**16**) was reduced to **17** and dehydrated to **18**. The same compound (**18**) was obtained from the known[19] olivetyl–pinene (**19**) by boiling in ethanol (in the presence of silver nitrate) or by irradiation. Free radical reactions on pinenes are known to cause opening of the cyclobutane ring.[20]

It is of interest that recently[21] compound **16** has been isolated on pyrolysis of cannabidiol (**1c**), from which it is formed by oxidative cyclization. A number of related reactions in other areas of organic chemistry have been described in the literature.[9,22]

The synthetic potential of the oxidative cyclization described in this paper led us to investigate this reaction in some detail. The following points were examined (for details see Experimental):

(a) *Oxygen.* On exclusion of oxygen from the irradiation vessel (by repeated vacuum evacuation of a frozen and then thawed solution of **1a** in alcohol or cyclohexane) no reaction was observed. Apparently oxygen is an absolute requirement for the reaction.

(b) *Light.* Comparison of the changes taking place in solutions of **1a** under intense sunlight, or under diffuse light (on a laboratory bench) and under the same conditions but protected from light, shows that the reaction takes place (after a month) only in the presence of light. Irradiation does not cause decarboxylation of the starting material or the products.

(c) *Heat.* Irradiation at 12° or 30° gave the same products, and in the same amounts. However, heating (without irradiation) at 80° causes decarboxylation, the rate of which is increased at higher temperatures.

(d) *Singlet oxygen.* The presence of singlet oxygen (generated according to Foot)[22] instead of light does not transform **1a** into **4b**, **6b**, **9** or **10** under the reaction conditions employed.

(e) *Reactivity of cannabidiolic acid methyl ester* (**1b**). This compound reacts essentially in the same way as the free acid (**1a**); The yields are, however, different (Table).

(f) *A radical initiator—manganese dioxide.*[24] Boiling **1b** in chloroform with manganese dioxide[25] gives the same compounds as those obtained on irradiation, except that no hydroperoxides are formed (Table). When oxygen was bubbled prior to the reaction both the yields and rate of reaction were improved. It is plausible that either the oxygen reoxidizes the reduced manganese compound (MnO?) formed in the reaction back to manganese dioxide, or more probably it reactivates the oxidant (present in excess). Active manganese dioxide is well known[25] for its tendency to deteriorate.

The above results indicate that the oxidative cyclization described in this paper is not solely a photochemical reaction, as assumed in our preliminary communication,[2] but a free radical one.

(g) *Reaction kinetics.* First order kinetics as regards **1a** are followed on irradiation of **1a** in cyclohexane, oxygen being bubbled throughout the reaction. This was determined by the decrease in concentration of the starting material (**1a**), the concentration of the second reactant (oxygen) being constant.

The reaction rate in the presence of 10% isopropanol in the solvent (cyclohexane) is *ca* 7 times faster than in its absence (specific rate constants, $k = 3{\cdot}0 \times 10^{-4}$ sec^{-1} and $k = 4{\cdot}0 \times 10^{-4}$ sec^{-1} respectively). It is possible that an isopropanol radical is formed first; then it serves as an efficient radical propagator.

The oxidative cyclization of **1a** to **4a** and **6a** probably takes place as shown in the Scheme. A radical initiator is assumed to produce a phenoxide radical which adds to the Δ^1 double bond, and causes formation of a radical on C_1. The termination of the process is apparently best achieved (under our experimental conditions) by the addition of ground state oxygen to the C_1 radical to form **9** and **10** which are reduced to **4a** and **6a**.

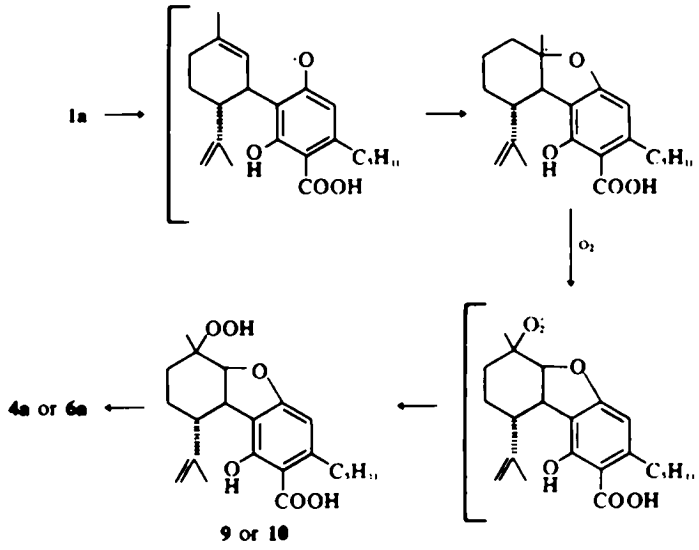
An alternative mechanism, based on a possible "ene" type addition[23] of oxygen to the Δ^1 double bond is excluded because, (a) singlet oxygen does not lead to the same compound (as the described above) and (b) the formation of *two* C_1 isomers would not be expected from the stereospecific addition generally observed[23] in this type of reaction.

We have not investigated in depth the scope of the oxidative-cyclization reaction described above.

Table. Reaction of cannabidiolic acid (**1a**) and its methyl ester (**1b**) on irradiation and with manganese dioxide

Starting material	Reagent[a]	Reaction time (h)	Solvent	Products (%)[b] Starting material	Compounds **7a**, **8** & X	Compounds **4b** & **9**	Compounds **6b** & **10**
1a	UV/O_2	160	cyclohexane	9	11	17	16
1b	UV/O_2	160	cyclohexane	9	4·8	34	25·5
1b	—	45	$CHCl_3$	80	4	traces	traces
1b	MnO_2/O_2	1	$CHCl_3$	traces	38[c]	20	14
1b	MnO_2	5	$CHCl_3$	50	24	6[e]	4[f]
1b	MnO_2	25	$CHCl_3$	10	45[d]	9[e]	5[f]
1b	MnO_2	11	$CHCl_3$	20	10[d]	21	16
4b	MnO_2	13	$CHCl_3$	95%	—	—	—
6b	MnO_2	13	$CHCl_3$	95%	—	—	—

[a]The irradiation experiments were performed at room temperature; the rest—on boiling. [b]Determined by isolation on preparative TLC (after esterification in case of **1a**); [c]Compound X (30%), **7a** (4%), **8** (4%). [d]X (32%), **7a** (6%), **8** (7%); [e]Only **4b** present; [f]Only **6b** present; [g]**7a** (1·5%), **8** (1·5%), X (7%).



SCHEME

It will be of interest to determine whether it is of general application. Another aspect which has to be clarified is whether the cannabielsoic acids are natural porducts or whether they are artifacts formed in hashish by oxidation of cannabidiolic acid. It is tempting to speculate that they are indeed natural products because, as described above, on experimental oxidation of cannabidiolic acid *both* cannabielsoic acid A (**4a**) and the 1-iso isomer (**6a**) are formed while in hashish we have not detected **6a**. In addition cannabielsoic acid B (**5a**) which is apparently not formed in the synthetic sequence is found in hashish in addition to **4a**. However, the low yields both in synthesis and on isolation from hashish make such a suggestion tenuous at present.

EXPERIMENTAL

Instrumentation, solvent purification, chromatography and irradiation conditions are described in the experimental part of our previous paper on the photochemistry of cannabinoids.[11]

Isolation of cannabielsoic acids. Hashish (400 g) of undetermined age (not less than 1 year old) of Lebanese origin was thoroughly extracted with light petroleum. Most of the cannabinoids were extracted with this solvent. The undissolved residue was extracted with boiling benzene (soxhlet) (1000 ml). The benzene soln was concentrated and washed 3 times with a 1:1 mixture of 2% $NaHSO_3$ aq and 5% NaOH aq. The basic soln was acidificed at 0° (10% H_2SO_4 aq) and extracted with ether (2 times, 150 ml). On evaporation of the solvent a gummy residue (11·2 g) was obtained which was chromatographed on silica gel (Merck) (550 g). Elution with light petroleum followed by 5% ether in light petroleum afforded only minute amounts of neutral material. Elution with 20% ether in light petroleum (3 liters) gave (in order of elution) **1a** (2·8 g), **2a** (0·67 g) and **3a** (0·45 g). Elution with ether and with EtOAc (81) afforded a mixture (4·50 g) which was chromatographed on silica gel (200 g). Elution with light petroleum (2 l) and ether (3 l) gave small amounts of unidentified mixtures; elution with ethyl acetate (3 l) gave a mixture which contained the cannabielsoic acids. These were purified by preparative thick layer chromatography. The plates were successively eluted with a mixture of benzene MeOH and AcOH (91:7:2) or with light petroleum, $CHCl_3$, AcOH(88:10:2). Three compounds were extracted with $CHCl_3$ and MeOH from the silica gel scraped from the plates: cannabidiolic acid (**1a**), *cannabielsoic acid A* (**4a**), m.p. 147–148° (chloroform–light petroleum), 0·32 g (0·08% in hashish), λ_{max}^{EtOH} 225 mμ (ε, 22500), 269 mμ (ε, 8720), 302 mμ (ε, 3700); ν($CHCl_3$) 1630, 1250, 892 cm^{-1}; NMR ($CDCl_3$) (δ): 0·90, 1·50, 1·83 (Me groups), 2·93 (br, t, 2H), 3·38 (1H, dd, $J_{2,3}$ = 5·2, $J_{3,4}$ = 9·0 Hz), 4·12 (1H, d, J = 5·2 Hz, C_3–H), 4·56 (2H, br, C=CH_2), 6·35 (1H, s, aromatic–H), 7·50 (2H, br, OH), 11·28 (1H, s, COOH); mass spectrum: 374, 356, 330, 247, 205, 161; (Found: C, 70·67; H, 7·35. $C_{22}H_{30}O_4$ requires: C, 70·58; H, 8·02%); *cannabielsoic acid B* (**5a**) 0·16 g (0·04% from hashish), m.p. 221–2°, λ_{max}^{EtOH} 226, 257, 284 mμ (ε, 15000, 4850, 2800), on addition of NaOH, 221, 281 (ε, 15000, 2900), ν($CHCl_3$) 1725 cm^{-1}; NMR ($CDCl_3$), (δ): 0·88, 1·51, 1·83 (Me groups), 2·95 (br, 2H), 3·45 (1H, dd, $J_{2,3}$ = 5·0, $J_{3,4}$ = 10·0 Hz, C_3–H), 4·35 (1H, d, J = 5·0 Hz, C_3–H), 5·02 (2H, s, C=CH_2), 5·45–6·00 (2H, exchangeable with D_2O), 6·40 (1H, s, aromatic–H), no protons on offset down to 16·0; mass spectrum: 330 (M^+–CO_2), 247, 205, 161, 147.

An alternative isolation was accomplished as follows: The benzene fraction of hashish (96 g) (obtained as described above) was separated into acidic (24 g) and neutral (57·6 g) fractions. The acidic material was dissolved in ether (1 l) and treated with excess of an etheral solution of diazomethane. After 5 min the solvent was removed and the residue was chromatographed on Florisil (1·5 kg). Light petroleum (4 l) and 1% ether in light petroleum (4 l) gave small amounts of oils. Successive elution with 2%, 5% and 10% ether in light petroleum gave **1b** (6·0 g), **2b** (1·2 g) and **3b** (0·96 g). Elution with ether (5 l) gave a mixture of cannabielsoic acids methyl esters (6·2 g)

which were separated by a further chromatography on Florisil (600 g).

Compound **4b** (1·6 g) was eluted with 10% ether in light petroleum; **5b** (1·1 g) was eluted with 50% ether in light petroleum. Further purification was accomplished by preparative TLC (elution with 30% ether in light petroleum), the ester B being considerably more polar than ester A. *Cannabielsoic acid A methyl ester* (**4b**) was obtained as an oil, mol. weight (mass spectrum), 388; $[\alpha]_D^{CHCl_3}$ + 183°; $\nu(CCl_4)$ 1660, 975 cm^{-1}; NMR ($CDCl_3$) (δ) 0·90 (t, 3H, terminal Me), 1·44 (s, 3H, C_1–Me), 1·83 (s, 3H, C_6–Me), 2·85 (2H, benzylic), 3·38 (dd, $J_{2,3}$ = 5·2, J = 9·0 Hz, C_3–H), 3·88 (s, 3H, $COOCH_3$), 4·12 (1H, d, J = 5·2, C_2–H), 4·52, 4·60 ($C{=}CH_2$), 6·25 (arom H), 11·28 (OH, exchangeable with D_2O).

Cannabielsoic acid B, methyl ester (**5b**) was crystallized from light petroleum, m.p. 58–60°; $[\alpha]_D^{CHCl_3}$ + 25°; $\nu(CCl_4)$ 3580, 1720 cm^{-1}; NMR ($CDCl_3$) (δ): 0·89, 1·46, 1·80 (Me groups), 2·72 (2H, t), 3·29 (1H, dd, $J_{2,3}$ = 6·0, $J_{3,4}$ = 10 Hz, C_3–H), 3·80 (3H, s, $COOCH_3$), 4·11 (1H, d, J = 6 Hz, C_2–H), 5·02 (2H, s, $C{=}CH_2$), 5·75 (1H, exchangeable with D_2O, OH), 6·28 (1H, aromatic-H), mass spectrum—388 (M^+, 20%), 370 ($M-H_2O$, 3%), 358 (10%), 275 (60%), 263 (100%), 231 (40%), 205 (20%).

Hydrolysis of the methyl esters of cannabielsoic acids A (**4b**) *and B* (**5b**)

The ester A **4b** (130 mg) was stirred for 20 h with a soln of KOH (220 mg) in MeOH (8 ml) and H_2O (2 ml), followed by boiling for 4 h. The soln was acidified (dil HCl) and extracted with $CHCl_3$ (3 × 15 ml) to give **4a** (80 mg), (80 mg), identical by IR, NMR and TLC to authentic material isolated from hashish.

The ester B **5b** (75 mg) under the same experimental conditions gave a mixture of starting material (31 mg) and the free acid **5a** (8 mg). When the reflux of 30 mg of ester **5b** was continued for 23 h only the acid (7 mg) was isolated.

Irradiation of cannabidiolic acid

A soln of **1a** (1·1 g) in cyclohexane (165 ml) stirred with a magnetic stirrer and a stream of O_2 (30–40 bubbles/min) was irradiated for 160 h with a Q81-Hanau lamp through a quartz or a Pyrex filter with Rose bengal as sensitizer. The irradiated mixture was cooled with cold water (8–12°). The reaction was monitored by GLC and the possibility of decarboxylation was checked by reacting aliquots with diazomethane and comparison by TLC with authentic samples of **1b** and **1c**. The solvent was evaporated under reduced pressure at 40–45°. The residue was checked for peroxides by dissolving aliquots in light petroleum and adding 3–4 drops of a soln of KI (50 mg) in H_2O (1 ml) and excess of starch and mixing well. A deep violet color developed immediately. At this stage 2 different routes were followed:

(i) *Reduction and separation of acids.* The residue was dissolved in $CHCl_3$ (10 ml) and the soln was shaken for 5 min with a $NaHSO_3$ soln (2 g in 50 ml H_2O). The aq phase was extracted with $CHCl_3$ (2 × 50 ml) and the combined organic phase was washed with H_2O. The residue now gave a negative test to KI-starch. The mixture was separated by preparative TLC (elution mixture: benzene, MeOH, AcOH in a ratio of 91:7:2). The silica gel was extracted with $CHCl_3$ and MeOH. The least polar compound was starting material; the two more polar compounds were cannabielsoic acid A (**4a**) and its C-1 isomer (**6a**). Cannabielsoic acid A (**4a**) was identified by direct comparison with an authentic sample. 1-*Isocannabielsoic* (**6a**), m.p. 162–5° (chloroform–light petroleum); λ_{max}^{EtOH} 224, 270, 302 mμ (ε, 25680, 10250, 4270); $\nu(CHCl_3)$ 1630, 1250, 895 cm^{-1}; NMR ($CDCl_3$) (δ): 0·92, 1·50 1·83 (Me groups), 2·94 (2H, t), 3·30 (1H, dd, $J_{2,3}$ = 5·2, $J_{3,4}$ = 10·0 Hz, C_3–H), 4·30 (1H, d, J = 5·2 Hz, C_2–H), 4·52, 4·62 (2H, $C{=}CH_2$), 6·34 (1H, aromatic), 7·20 (2H, b, exchangeable with D_2O), 11·22 (1H, exchangeable D_2O). Mass spectrum: 374, 356, 330, 247, 205. (Found: C; 70·60; H, 7·91. $C_{22}H_{30}O_3$ requires: C, 70·58; H, 8·02%).

(ii) *Separation of esters.* The residue was dissolved in dry ether (100 ml) and an ether soln of CH_2N_2 was slowly poured in until the typical yellow color of CH_2N_2 persisted. After standing 5 min at room temp the solvent was evaporated and the residue was separated on preparative TLC plates, (20% ether in light petroleum 3 successive runs). The silica gel was extracted with ether (3 × 25 ml). Six distinct fractions were obtained with R_f values of 0·93, 0·86, 0·52, 0·39, 0·32 and 0·23. *The least polar fraction* (R_f 0·93) (120 mg) was negative in the KI-starch test. It was further separated into 3 components (in the ratio of 4:1:2) by preparative TLC (light petroleum 6 successive runs):

(1) *Δ⁸-Iso-tetrahydrocannabinolic acid, methyl ester* (**7a**), R_f 0·61; mol. weight (mass spectrum), 372; λ_{max}^{EtOH} 222 (ε, 18600), 273 (ε, 11400), 304 mμ (ε, 4650); $\nu(CCl_4)$ 1630, 890 cm^{-1}; NMR (CCl_4) (δ): 0·91 (t, 3H), 1·30, 1·90 (Me group), 2·80 (2H, t), 3·55 (t, C_3–H), 3·89 (s, $COOCH_3$), 4·85 (2H, $C{=}CH_2$), 6·09 (1H, arom).

(2) *The dehydrated cannabielsoic acid methyl ester derivative* **8**, R_f 0·58, mol. weight (mass spectrum) 370; λ_{max}^{EtOH} 222 (ε, 21000), 230 (ε, 19500), 276 (ε, 12000), 300 mμ (sh) (ε, 5100); $\nu(CCl_4)$ 1635, 890 cm^{-1}; NMR ($CDCl_3$) (δ): 0·90 (t, 3H, terminal Me) 1·82, 1·90 (both s, 3H, olefinic Me), 2·84 (2H, benzylic), 3·40 (dd, 1H, C_3–H), 3·88 (s, 3H, $COOCH_3$), 4·50, 4·60 ($C{=}CH_2$), 4·75 (d, 1H, J = 7 Hz, C_2–H), 5·80 (b, 1H, C_6–H), 6·22 (1H, arom), 11·40 (OH, exchangeable with D_2O).

(3) A compound, whose structure *is unknown* (compound X), R_f 0·53, mol. weight (mass spectrum) 372; λ_{max}^{EtOH} 222 mμ (ε, 16950), 231 (ε, 15680), 237 (ε, 15300), 277 (ε, 10300), 301 mμ (sh) (ε, 4100); $\nu(CCl_4)$ 1650, 1275 cm^{-1}; NMR (CCl_4) (δ): 0·9–1·00 (12H, 4 methyls), 2·15 (1H), 2·85 (b, 2H), 3·85 (1H, dd, J = 6·0, J = 10·5 Hz), 3·88 ($COOCH_3$), 4·85 (1H, d, J = 10·5 Hz), 6·11 (1H, arom), 11·29 (1H, exchangeable D_2O). This compound gives a monoacetate.

(4) *The fraction with* R_f 0·86, 100 mg (negative KI-starch test) was shown to be the methyl ester of the starting material (direct comparison of IR and NMR spectra).

(5) *The fraction with* R_f 0·52 (88 mg) showed a positive KI-starch test. It was identified as the *hydroperoxide* **9**, mol. weight (mass spectrum) 404 (very weak), 388 (404–16); $[\alpha]_D^{CHCl_3}$ + 167°; λ_{max}^{EtOH} 221, 227, 232, 274, 303 mμ (ε, 19200, 18330, 16850, 10000, 4000); $\nu(CCl_4)$ 1650, 1280, 890, 835 cm^{-1} (O–O vibration); NMR (CCl_4) (δ): 0·92 (t, 3H), 1·46 (s, 3H, C_1–Me), 1·78 (s, 3H, C_6–Me), 2·85 (2H, benzylic), 3·30 (dd, 1H, C_3–H) 3·88 (s, 3H, $COOCH_3$), 4·30–4·60 (3H, $C{=}CH_2$ and C_2–H), 6·17 (1H, arom), 8·05, 11·3 (2H, OOH and OH, exchangeable with D_2O).

(6) *The fraction with* R_f 0·39 (68 mg) also showed a positive KI-starch test. It was identified as the *hydroperoxide* **10**, mol. weight (mass spectrum) 404 (very weak), 388 (404–16); $[\alpha]_D^{CHCl_3}$ + 193°; λ_{max}^{EtOH} 222, 227, 232, 273, 303 mμ (ε, 19250, 18450, 16160, 10350, 4040); $\nu(CCl_4)$ 1650, 1275, 895, 845 cm^{-1} (O—O vibration); NMR (CCl_4)

(δ): 0·9 (t, 3H, terminal Me), 1·41 (s, 3H, C_1–Me), 1·79 (s, 3H, C_6–Me), 2·77 (2H, benzylic), 3·18 (dd, 1H), C_3–H), 3·86 (s, 3H, $COOCH_3$), 4·36–4·63 (3H, $C{=}CH_2$ and C_7–H), 6·17 (1H, arom), 8·36, 11·27 (2H, OOH and OH, exchangeable with D_2O).

(7) *The fraction with* R_f 0·32 (108 mg) was negative in the KI-starch test. It was identified as **6b**, the C_1 isomer of **4b**, the methyl ester of the natural cannabielsoic acid A; mol. weight (mass spectrum) 388; $[\alpha]_D^{MeOH}$ + 168°; $\nu(CCl_4)$ 1650, 1275, 892 cm^{-1}; NMR ($CDCl_3$) 0·91 (t, 3H, terminal Me), 1·35 (s, 3H, C_1–Me), 1·82 (s, 3H, C_6–Me), 2·88 (2H, benzylic), 3·30 (1H, dd, $J_{2,3}$ = 5·5, $J_{3,4}$ = 10 Hz, C_3–H), 3·90 (s, 3H, $COOCH_3$), 4·27 (1H, d, J = 5·5 Hz, C_2–H), 4·55, 4·64 ($C{=}CH_2$), 6·28 (1H, arom), 11·30 (OH, exchangeable with D_2O).

(8) *The fraction with* R_f 0·23 (99 mg) was also negative in the KI-starch test. It was shown to be identical (IR, TLC, NMR) with the methyl ester of cannabielsoic acid A (**4b**), $[\alpha]_D$ + 161° (apparently not very pure). Compound **4b** gives a monoacetate (**4c**) which was purified by preparative TLC (ether : light petroleum, 1 : 1), $\nu(CCl_4)$ 1775, 1700, 900 cm^{-1}; NMR (CCl_4), (δ) 0·9, 1·28, 1·70, 2·10 (4 CH$_3$ groups), 2·62 (2H), 3·15 (dd, $J_{2,3}$ = 5·2; $J_{3,4}$ = 9·8 Hz, C_3–H); 3·75 (s, 3H, $COOCH_3$); 3·95 (d, $J_{2,3}$ = 5·2 Hz, C_2–H), 4·50, 4·65 (2H, $C{=}CH_2$), 6·47 (1H, arom).

Conversion of peroxide **9** *to cannabielsoic acid Me ester* (**4b**)

This reduction was performed in 3 ways:

(i) Treatment with $NaHSO_3$ as described above (see "Irradiation of cannabidiolic acid").

(ii) Heating **9** (40 mg) in CCl_4 for 2 h gave 36 mg **4b**.

(iii) Irradiation of **9** (8 mg) in 1 ml cyclohexane in a test tube attached to the well of an irradiation vessel for 7 h gave 7 mg **4b**. In all cases identity was established by TLC, IR and NMR.

Using the same procedures the peroxide **10** was converted into **6b**.

Cannabielsoic acid methyl ester (**4b**) and **6b** remained unchanged on heating or irradiation under the above conditions.

Dehydration of cannabielsoic acid methyl ester (**4b**) *and 1-iso-cannabielsoic acid methyl ester* (**6b**)

Compound **4b** (31 mg) was dissolved in pyridine (1 ml) and the soln was cooled in an ice bath. Thionyl chloride (0·1 ml) was added. The mixture was poured into ice-water (10 ml) after 1 min and extracted with ether. The organic layer was washed with NaHCO$_3$ aq, dried over Na_2SO_4 and evaporated. The oily residue was purified on preparative TLC (5% ether in light petroleum) to give 15 mg of **8**.

Dehydration of **6b** (27 mg) under the same conditions, or for 15 min, gave a mixture, which was partially separated by preparative TLC (5% in petroleum ether). After 3 successive runs two materials were isolated; the less polar fraction (R_f 0·73) (10 mg) is apparently a mixture of the isomers **11a** and **11b** (in an approximate ratio of 1 : 3) on the basis of its NMR spectrum: $\delta(CCl_4)$, 0·90 (terminal Me), 1·70, 1·85, 1·90 (olefinic Me), 2·80 (benzylic H), 3·10–3·30 (C_3–H in **11b**) 3·88, 3·90 ($COOCH_3$), 3·85 (C_3–H in **11a**), 4·65, 4·80 ($C{=}CH_2$ in **11a** and **11b**, and C_2–H in **11b**), 5·35 (C, methylene in **11b**), 6·18 (arom in **11a**) 6·70 (arom in **11a**) 6·70 (arom in **11b**), 11·25, 11·65 (in ratio of 3 : 1, exchangeable with D_2O).

The more polar fraction (R_f 0·65) (7 mg) was shown to be identical (IR and NMR) with **8** obtained from the dehydration of **4b** as described above.

Catalytic reduction and dehyration of cannabielsoic acid methyl ester (**4b**)

A soln of **4b** (50 mg) in EtOH (5 ml) was hydrogenated with Adam's catalyst. One equiv of H_2 was absorbed in 5–6 min. The catalyst was filtered, the solvent was evaporated. The material obtained, *dihydrocannabielsoic acid, methyl ester* (**12**) was purified by preparative TLC (5% ether in light petroleum) to give an oil, NMR ($CDCl_3$), δ, 0·9 (3H), 0·95 (6H, d) 1·43 (3H, C_1–Me), 2·85 (2H, benzylic), 3·22 (1H, dd, $J_{2,3}$ = 5·2, $J_{3,4}$ = 10·5 Hz, C_3–H), 3·90 (3H, $COOCH_3$), 4·11 (1H, d, J = 5·2 Hz, C_2–H), 6·29 (1H, arom), 11·60 (OH).

This material (30 mg) was dehydrated as described above. TLC data indicated that essentially one compound only was obtained. It was purified by preparative TLC (30% ether in light petroleum). The compound **13** obtained was an oil, $\nu(CCl_4)$ 1655, 1285 cm^{-1}; NMR ($CDCl_3$), δ 0·9 (3H), 0·96 (6H, d) 1·88 (s, olefinic CH_3), 2·84 (benzylic 2H), 3·23 (1H, dd, $J_{2,3}$ = 7·0, $J_{3,4}$ = 11 Hz, C_3–H), 3·90 (3H, $COOCH_3$), 4·74 (1H, d, J = 7 Hz, C_2–H), 5·81 (1H, b, olefinic), 6·24 (aromatic H), 11·65 (OH).

Catalytic reduction and dehydration of 1-iso-cannabielsoic acid methyl ester (**6b**)

A soln of **6b** (105 mg) was hydrogenated as described above. The compound (95 mg) obtained, *dihydro-iso-cannabielsoic acid* (**14**) showed one spot on TLC. It is an oil, $\nu(CCl_4)$ 1655, 1265 cm^{-1}; NMR ($CDCl_3$), δ, 0·87 (3H), 0·89 (6H, d), 1·28 (3H, C_1–Me), 2·65–3·20 (3H, mult., benzylic and C_3–H), 3·90 (3H, $COOCH_3$), 4·20 (1H, d, J = 5 Hz, C_2–H), 6·24 (1H, arom), 11·50 (OH). Without further purification 40 mg of **14** were dehydrated with thionyl chloride in pyridine as described above. The product (32 mg) exhibited numerous spots on TLC analysis. It was purified by preparative TLC (5% ether in light petroleum). Only two products were obtained in fairly pure form (TLC data only). The more polar one (7 mg, R_f 0·60) was shown to be identical (TLC, IR, NMR) with **13** obtained as sole product of the reduction and dehydration of **4b**. The less polar product (9 mg) (R_f 0·67) is assumed to be a mixture of **15a** and **15b** (in a ratio of 3 : 1). It is an oil, δ 0·9 (terminal CH_3), 1·0 (6H, isopropyl), 1·70 (3H, olefinic CH_3), 2·60–3·00 (2H, benzylic and C_3–H in **15b**), 3·60–3·80 (C_3–H in **15a**), 3·90 (3H, $COOCH_3$ in **15a**), 3·93 (3H, $COOCH_3$ in **15b**) 4·85 (C_2–H in **15b**), 5·40 (C, methylene in **15b**), 6·25 (arom H in **15a**), 6·80 (arom H in **15b**), 11·90, 12·05 (in a ratio of 3 : 1, exchangeable with D_2O); mol. weight (mass spectrum) 372.

Conversion of cannabielsoic acid A (**4a**) *into compound* **18**

Cannabielsoic acid (130 mg) was heated and distilled over a period of 1 h at 190° (0·5 mm). The yellow oil obtained (63 mg) showed two main spots on TLC (50% ether in light petroleum). On preparative TLC purification (50% ether in light petroleum) **16** (20 mg) was obtained as an oil, $\nu(CCl_4)$ 3600 cm^{-1}; $[\alpha]_D^{EtOH}$ + 94°; NMR ($CDCl_3$), δ, 0·89, 1·46, 1·82 (CH_3 groups) 2·50 (2H), 3·30 (C_3–H, dd, $J_{2,3}$ = 6 Hz, $J_{3,4}$ = 10·5 Hz), 4·08 (C_2–H, d, J = 6 Hz), 5·02 (2H, $C{=}CH_2$), 6·22 (2H, aromatic). Without further purification, 35 mg of **16** in ethanol (5 ml) were hydrogenated at room pressure with platinium dioxide as catalyst. On evaporation of the solvent, **17** was obtained as an oil,

δ(CDCl$_3$), 0·90, 0·95 (d, J = 6 Hz), 1·45 (CH_3 groups), 2·50 (2H), 3·10 (C_3–H, dd, $J_{2,3}$ = 5·5 Hz, $J_{3,4}$ = 9·5 Hz), 4·05 (C_2–H), d, J = 5·5 Hz), 6·16, 6·30 (aromatic H). Without further purification **17** was dehydrated by dissoving in pyridine (0·5 ml), cooling to 0°, addition of thionyl chloride (2 drops) and addition of ice after 1 min. The mixture obtained was purified by preparative TLC (elution with 5% ether in light petroleum, 3 runs R_f 0·5) to yield **18**, 12 mg, identical to the product obtained from olivetyl–pinene (**19**) by heating with silver nitrate or irradiation (*vide infra*). The comparisons were performed by TLC, GLC, IR and NMR.

Isomerization of **19** *to* **18**

1. *By heating.* Olivetyl–pinene, $[\alpha]_D^{EtOH}$ – 87°, (370 mg) and silver nitrate (100 mg) in abs EtOH (30 ml) or benzene were boiled under reflux for 3 h. The solvent was evaporated. The residue was taken up in benzene and purified by preparative TLC (elution with 10% ether in light petroleum). Compound **18** has $[\alpha]_D^{EtOH}$ + 71°; λ_{max}^{EtOH} 220, 275, 284 mμ (ε, 12500, 1000, 1043); NMR (in CCl_4), δ, 0·90, 0·94 (d, J = 6 Hz), 1·85 (CH_3 groups), 2·42 (2H, t), 3·05 (C_3–H, q, $J_{2,3}$ = 6 Hz, $J_{3,4}$ = 9 Hz), 4·56 (C_2–H, d, J = 6 Hz), 5·10 (OH), 5·68 (C_4–H, br), 5·95, 6·10 (aromatic H); mol. weight (mass spectrum 314); (Found: C, 80·50; H, 9·42. $C_{21}H_{30}O_2$ requires: C, 80·21; H, 9·62%).

2. *By irradiation.* A soln of olivetyl–pinene (0·55 g) in CH_3OH (150 ml) stirred with a magnetic stirrer under N_2 was irradiated with a Q 81-Hanau lamp through a quartz glass and corex filter for 24 h. The residue from the irradiation was chromatographed on Florisil (50 g) and the fractions which were washed with light petroleum and 1% ether in light petroleum (180 mg) were further separated on preparative TLC plates. The plates were eluted by a mixture of 10% ether in light petroleum (3 successive runs). The least polar fraction (50 mg) was shown to be identical with **18** (TLC, VPC, IR and NMR). It is interesting to note that under the same conditions the R_f on TLC is identical with that of the natural product cannabicyclol, while its retention time on GLC is identical with that of the starting material.

Irradiation of cannabidiolic acid methyl ester (**1b**)

This reaction was performed on 1 g **1b** exactly as described for **1a**. The following compounds (or mixtures) were obtained after chromatography on preparative TLC (20% ether in light petroleum, 2 runs): A mixture (48 mg) of **7**, **8** and the unknown material (compound X) mentioned previously (R_f 0·95); starting material (90 mg) (R_f 0·92); (R_f 0·92); compound **9g**) (R_f 0·55); compound **10** (180 mg) (R_f 0·47); compound **6b** (75 mg) (R_f 0·35); compound **4b** (134 mg) (R_f 0·24).

Oxidation of cannabidiolic acid methyl ester (**1b**) *with* MnO_2 *and/or* O_2

A suspension of **1b** (700 mg) and freshly prepared MnO_2[23] (11 g) in chloroform (100 ml) were boiled for 25 h. During the reaction (after 6 h) additional 5 g MnO_2 were added. The mixture was cooled, filtered and evaporated. The following compounds were isolated after chromatography (as described above): starting material (70 mg), **4b** (60 mg), the isomeric **6b** (35 mg) and a mixture (336 mg) of **7a**, **8** and the previously mentioned unidentified product X. Compounds **7a** and **8** represent 12% and 17% respectively of this mixture.

The above reaction was repeated (for 11 h) in the absence of manganese dioxide, O_2 being bubbled through the soln prior to the reaction, which was conducted under an O_2 atmosphere. The following compounds were identified (preparative TLC): compound **7a** (1·5%), compound **8** (1·5%), compound X (7%), starting material (20%), compounds **4b** and **9** together (21%) and compounds **6b** and **10** together (16%).

The above reaction was repeated (for 1 h) in the presence of MnO_2 (7·5 g); O_2 was bubbled through the soln prior to the reaction, which was conducted under an O_2 atmosphere. The following compounds were identified (preparative TLC): compound **7a** (4%), compound **8** (4%), compound X (30%), compounds **4b** and **9** together (20%) and compounds **6b** and **10** together (14%).

Compounds **4b** and **6b** (50 mg each) were found to be stable to manganese dioxide (500 mg) (boiling under reflux in $CHCl_3$ for 13 h).

Thermal treatment of cannabidiolic acid (**1a**) *and its methyl ester* (**1b**)

Cannabidiolic acid **1a** (100 mg) was boiled in different solvents (50 ml) for 2 h under N_2. The following results were obtained: methylene chloride, $CHCl_3$ or tetrahydrofuran—no change; benzene or toluene–partial decarboxylation to cannabidiol; xylene or n-dibutyl ether—full decarboxylation to cannabidiol. When **1b** (150 mg) in $CHCl_3$ (15 ml) was boiled for 5 h (air not excluded) compounds **7a** and **8** were formed in 2–3% yields. When the boiling was continued for 44 h **4b** and **6b** were formed (TLC) in addition to **7a** and **8**. Most of the starting material (80%) was recovered unchanged.

Effects of various parameters on the oxidative cyclization of **1a** *or* **1b**

Light. Cannabidiolic acid **1a** (50 mg) in cyclohexane, 96% EtOH or abs EtOH (6 ml) in closed Pyrex test tubes were placed in the sun (20–25°) and on a laboratory bench. Half of the test tubes were well protected with Al foil. After a week the test tubes were opened. The contents of the protected test tubes were unchanged (TLC, GLC, KI-starch test). The material in the non-protected test tubes was found to have produced the 8 compounds described in the irradiation reaction.

Oxygen. A soln of **1a** (40 mg) in cyclohexane was freezed in liquid N_2 and the gas content of the ampule was evacuated (oil pump, 0·1 ml Hg). The soln was thawed and evacuated again. This freeze–thaw cycle was repeated 4 times. A sealed ampule thus treated was irradiated; a second one was left in the sun for a week. When opened neither soln had changed. Controls (not under vacuum) gave the 8 compounds discussed previously (TLC, GLC, KI-starch test).

Singlet oxygen. Compound **1b** gave no **4b**, **6b**, **9** and **10** when reacted with singlet oxygen prepared from H_2O_2 and NaOCl or $Ca(OCl)_2$. As controls, singlet oxygen reactions described in the literature[21] could be reproduced.

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